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| EXAMINER | |
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| ALSTRUM ACEVEDO, JAMES HENRY | |
| **ART UNIT** | **PAPER NUMBER** |
| 1616 | |

DATE MAILED: 11/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/646,363 | ZENG, XIAN-MING | |
| | Examiner | Art Unit | |
| | James H. Alstrum-Acevedo | 1616 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *9/1/2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☒ Claim(s) *13 and 14* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

**Claims 1-15 are pending.** Receipt and consideration of Applicant's amended claims and remarks/arguments, submitted on September 1, 2006 is acknowledged.

### *Priority*

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

### *Specification*

The objection to the disclosure because of the informalities described on page 3 of the previous office action mailed on March 27, 2006 have been corrected by Applicant's amendment to the specification.

Claim 13 is objected to because of the following informalities: the word "dihydrate" is misspelled as "dehydrate" on line 4. Appropriate correction is required.

Claim 14 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n).

### *Claim Rejections - 35 USC §.112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

**Claims 6-9, 12, and 14-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

Claims 6-9 and 12 are vague and indefinite because these make reference to derivatives of an anti-inflammatory steroid (claim 6), such as budesonide (claims 7 and 12), a bronchodilator (claim 8), such as formoterol (claim 9). Applicant has not clearly defined the metes and bounds of the term "derivative" as it may apply to anti-inflammatory steroids (e.g. budesonide) or bronchodilators (e.g. formoterol). It is noted that in [0028] of the specification Applicant states, "Pharmaceutically acceptable derivatives include pharmaceutically acceptable salts..." However, this is not a definition, it is merely an example of a suitable derivative.

***Claim Rejections - 35 USC § 102***

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

**Claims 11 and 13-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Keller et al. (WO 00/28979, wherein U.S. Patent No. 6,645,466 is being used as the English language equivalent).**

Applicant claims (1) a dry powder inhalation product that is a product-by-process, said product comprising a first particulate medicament ("1st med."), carrier, and a second particulate medicament ("2nd med."), wherein the carrier/1st med. ratio is greater than the carrier/2nd med. ratio; the 1st med. is budesonide or an acceptable derivative thereof; the 2nd medicament is formoterol fumarate dihydrate, (2) a MDPI (multidose dry powder inhaler) comprising a composition according to claims 11-13.

**NOTE:** Claims 11 and 13 are product-by-process claims. The recited process steps used to describe the claimed product do not modify the structural characteristics of the instant products and therefore are given no patentable weight in examination. See MPEP §2113.

Keller discloses a dry powder composition with improved moisture resistance in Example 8 consisting of 0.2% w/w formoterol fumarate dihydrate (2nd med.), 0.5 % w/w glycopyrrolate (1st med.), 0.5% w/w magnesium stearate (excipient), and 98.8% w/w of lactose monohydrate (carrier) (Example 8; col. 14, lines 35-41). Both formoterol fumarate dihydrate and glycopyrrolate are known medicaments. Keller states,

> "In principle, **the constituents can be mixed with one another in any desired sequence**, where, however, mixing should expediently be carried out in such a way that the particles of the constituents--apart from the adhesion to the carrier particles--are essentially retained as such, i.e. are not destroyed, for example, by granulation and the like (col. 8, lines 53-59)."

Keller discloses that the dry powder formulations can be used in all customary dry powder inhalers and are particularly advantageously for use in **multidose dry powder inhalers** (i.e. MDPI), which contain a powder reservoir (col. 9, lines 3-8). Keller discloses that it is preferred to use magnesium stearate in dry powder formulations containing a betamimetic (e.g. formoterol), and/or an anticholinergic (e.g. glycopyrrolate), and/or a corticosteroid (e.g. budesonide) (col. 6, lines 52-54). Other suitable medicaments for use in Keller's composition are disclosed in col. 6, lines 13-33). Keller discloses that the ingress of moisture in multidose dry powder inhalers (MDPI) is a problem because it results in a dramatic fall in the in vitro fine particle dose and fine particle dose of pharmaceutical dry powders contained within said MDPI (col. 3, line 60 through col. 4, line 14).

The Examiner has considered the Applicant's data presented in Tables 1-4 of the specification. Said data does not demonstrate that the process steps used to make the claimed products modify the structural characteristics of the claimed dry powder compositions. Therefore, this rejection is proper. Applicant's claims 11 and 13-14 are open to a broad range of first and second medicament amounts and proportions. Even if Applicant's data in Tables 1-4 were somehow indicative of structural modification, this ground of rejection would still be proper because applicant's data was demonstrated with only 100:6 and 200:6 proportions of budesonide and formoterol fumarate dihydrate, wherein the total medicament concentration was in the range of about 5 wt%. The claims are readable on (i) structurally different medicaments, (ii) much higher or lower total concentrations of medicaments, and (iii) much lower or higher weight ratios of first medicament to second medicament, e.g. 100,000,000:1 or 1:0.99,999. It is the Examiner's position that Keller's disclosed method of mixing the composition constituents would necessarily produce a dry powder that cannot be distinguished from the dry powder encompassed by applicant's broad claim language

**Claims 11-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Trofast (U.S. Patent No. 6,030,604) ("Trofast").**

Applicant claims (1) a dry powder inhalation product that is a product-by-process, said product comprising a first particulate medicament ("1$^{st}$ med."), carrier, and a second particulate medicament ("2$^{nd}$ med."), wherein the carrier/1$^{st}$ med. ratio is greater than the carrier/2$^{nd}$ med. ratio; the 1$^{st}$ med. is budesonide or an acceptable derivative thereof; the 2$^{nd}$ medicament is formoterol fumarate dihydrate, (2) a MDPI (multidose dry powder inhaler) comprising a

composition according to claims 11-13, and (3) a method of administration comprising inhalation from a MDPI of a composition of any one of claims 11-13.

**NOTE:** Claims 11-13 are product-by-process claims. The recited process steps used to describe the claimed product do not modify the structural characteristics of the instant products and therefore are given no patentable weight in examination. See MPEP §2113.

Trofast discloses dry powder formulations for inhalation (title, abstract) that may be administered using any known dry powder inhaler, such as a **multidose inhaler**, wherein the inhaler may be a **dry powder inhaler** (col. 3, lines 20-23), and said formulations are useful for the treatment of respiratory disorders (e.g. asthma) (col. 3, lines 26-28). Trofast discloses in Example 6 a dry powder composition comprising **5.2 parts formoterol fumarate dihydrate, 896.8 parts lactose monohydrate (carrier), and 98 parts budesonide**, wherein the lactose and formoterol are mixed, micronized, and treated according to the method of WO 95/05805; budesonide is added, and the mixture is remixed, remicronized, and agglomerated. Trofast discloses that when formoterol and budesonide are present in the same dry powder formulation the molar ratio of formoterol to budesonide ranges from 1: 2,500 to 12: 1, preferably 1: 133 to 1: 6 (col. 2, lines 14-49). This corresponds to a formoterol to budesonide mass ratio, based on the molecular masses of formoterol fumarate dihydrate (496.513 g/mol) and budesonide (430.534 g/mol), ranging from approximately 1.153: 2,500 to approximately 13.8: 1, preferably from approximately 1.153: 133 to approximately 1.153: 6.

The Examiner has considered the Applicant's data presented in Tables 1-4 of the specification. Said data does not demonstrate that the process steps used to make the claimed products modify the structural characteristics of the claimed dry powder compositions.

Therefore, this rejection is proper. Applicant's claims 11-15 are open to a broad range of first and second medicament amounts and proportions. Even if Applicant's data in Tables 1-4 were somehow indicative of structural modification, this ground of rejection would still be proper because applicant's data was demonstrated with only 100:6 and 200:6 proportions of budesonide and formoterol fumarate dihydrate, wherein the total medicament concentration was in the range of about 5 wt%. The claims are readable on (i) structurally different medicaments, (ii) much higher or lower total concentrations of medicaments, and (iii) much lower or higher weight ratios of first medicament to second medicament, e.g. 100,000,000:1 or 1:0.99,999. It is the Examiner's position that Trofast's disclosed method of mixing the composition constituents would necessarily produce a dry powder that cannot be distinguished from the dry powder encompassed by applicant's broad claim language

***Claim Rejections - 35 USC § 103***

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The rejections of (1) claims 1-15 under 35 U.S.C. 103(a) as being unpatentable over Trofast (U.S. Patent No. 6,030,604); (2) claims 1-12 under 35 U.S.C. 103(a) as being unpatentable over Sarlikiotis et al. (U.S. Patent No. 6,284,287); and (3) claims 13-15 under 35 U.S.C. 103(a) as being unpatentable over of Sarlikiotis et al. (U.S. Patent No. 6,284,287) in view Clarke et al. (US 2002/0103260) **are withdrawn**, per Applicant's persuasive arguments described on pages 6-12 of the remarks/arguments.

**Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Trofast (U.S. Patent No. 6,030,604) in view of Keller et al. (WO 00/28979, wherein U.S. Patent No. 6,645,466 is being used as the English language equivalent).**

***Applicant Claims***

Applicant claims a method of preparing a dry powder inhalation composition comprising the steps of (a) mixing a carrier with a first portion of a first particulate medicament to obtain a first mixture (b) mixing said first mixture with a second particulate medicament to obtain a second mixture, and (c) mixing said second mixture with a second portion of the first medicament to form a dry powder inhalation composition, wherein the ratio by weight of the 2nd medicament/carrier ratio is less than the ratio by weight of the 1st medicament to the carrier.

***Determination of the Scope and Content of the Prior Art (MPEP §2141.01)***

The teachings of Trofast have been set forth above. The teachings of Keller have been set forth above.

***Ascertainment of the Difference Between Scope the Prior Art and the Claims***

***(MPEP §2141.012)***

Trofast lacks an explicit teaching about the order of steps used in preparing the dry powders. This deficiency is cured by the teachings of Keller.

***Finding of Prima Facie Obviousness Rational and Motivation***
***(MPEP §2142-2143)***

It would have been obvious to a person of ordinary skill in the art to combine the teachings of Trofast and Keller, because Keller teaches moisture resistant dry powder formulations comprising betamimetics in combination with anticholinergics and/or corticosteroids. An ordinary skilled artisan would have been motivated to combine the teachings of Trofast and Keller to obtain dry powder formulations comprising betamimetics that are moisture resistant and are present in the form of a salt or ester, such as formoterol fumarate. An ordinary skilled artisan would have also been motivated to combine the prior art teachings of Trofast and Keller, because both inventors teach inhalable dry powder compositions comprising betamimetics and the inclusion of magnesium stearate in Trofast's compositions would be expected to provide these with improved storage stability, and a reduced influence of penetrating moisture on the fine particle fraction (FPF) and fine particle dose (FPD) of said dry powders. An ordinary skilled artisan would have had a reasonable expectation of success upon combination of the prior art references because both teach the preparation of dry powder formulations comprising the mixing of dry particulate active(s) with particulate carrier (e.g. lactose). Regarding the order in which the different components are combined, Keller teaches that the different ingredients can be mixed in any desired sequence. This teaching encompasses

the following sequence of steps: blending a portion of 1st active particles with carrier particles to obtain a 1st mixture; combination of a 2nd active with the 1st mixture to obtain a second mixture; and finally admixture of the remaining 1st active particles to obtain a dry powder formulation. Mixing particulate components to obtain a dry powder composition is known as demonstrated by the cited prior art references.

Regarding claim 4, the amounts of active taught by Keller and Trofast would be sufficient to form a monolayer of each of these onto the carrier particles. Using the equation on page 5 of the instant specification, and the approximation that the particle sizes taught by Keller in terms of mass median aerodynamic diameter (MMAD) for the carrier (200 microns) and active particles (5 microns) are comparable to particle sizes expressed as volume median diameters, the Examiner has concluded that only 0.09 % of active is needed to form a monolayer on the carrier. The amount of actives taught by both Keller and Trofast meet this requirement. Therefore, an ordinary skilled artisan would have had reasonable expectation that mixing of the actives in the amounts taught by both references would obviously result in a coating of at least a monolayer onto the carrier particles.

Applicant has presented data in the instant specification (Tables 1-4) demonstrating the homogeneity of dry powders produced using Applicant's claimed method. This data is not convincing regarding the patentability of the claimed method, because it lacks a comparison of Applicant's method with the methods of the prior art. Applicant's claims 1-9 are open to a broad range of first and second medicament amounts and proportions. Even if Applicant's data in Tables 1-4 were somehow indicative of structural modification, this ground of rejection would still be proper because applicant's data was demonstrated with only 100:6 and 200:6 proportions

of budesonide and formoterol fumarate dihydrate, wherein the total medicament concentration was in the range of about 5 wt%. In other words, Applicant's data is not commensurate in scope with what is being claimed in the cited claims, because these recite broad ranges and claim 10 is not limited to a specific 1st and 2nd medicament mixed with carrier. Claims 1-6, 8, and 10 are readable on (i) structurally different medicaments, (ii) much higher or lower total concentrations of medicaments, and (iii) much lower or higher weight ratios of first medicament to second medicament, e.g. 100,000,000:1 or 1:0.99,999. The term "bronchodilator" may refer to a broad range of structurally different compounds (e.g. betamimetics and anticholinergics), which although exhibiting bronchodilating effects have different mechanisms of action and secondary biological activities. The term anti-inflammatory steroid" is also broad and can refer to a great variety of compounds having a steroidal core, but differing in the degree, and sometimes the kind of biological activity exhibited, in addition to anti-inflammatory effects. Similarly, claims 7 and 9 are readable on compositions with (i) structurally different 2nd medicaments (claim 7) or 1st medicaments (claim 9), (ii) much higher or lower total concentrations of medicaments, and (iii) much lower or higher weight ratios of 1st medicament to 2nd medicament. It is the Examiner's position that Trofast's disclosed method of mixing the composition constituents would necessarily produce a dry powder that cannot be distinguished from the dry powder encompassed by applicant's broad claim language. Furthermore, these data do not demonstrate that the prior art methods do not yield dry powder formulations exhibiting the same or substantially similar physical properties/characteristics.

**Claims 1, 5-8, and 11-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Walz et al. (US RE 38,912) in view of Keller et al. (WO 00/28979, wherein U.S. Patent No. 6,645,466 is being used as the English language equivalent).**

*Applicant Claims*

Applicant's claims have been described above in the instant office action.

*Determination of the Scope and Content of the Prior Art (MPEP §2141.01)*

The teachings of Keller have been set forth above. Walz teaches a process for preparing **powder formulations for inhalation** characterized by a high degree of homogeneity in the sense of uniformity of content (title, abstract, col. 1, lines 45-49), including powders comprising **two or more active compounds**. Said process comprises screening N+m roughly equal portions of excipient or excipient mixture with O roughly equal portions of one active substance component and P roughly equal portions of the other active substance component into the mixing apparatus in alternate layers. The number of fractions P and O may be selected, for example, so that P+O=N (col. 6, lines 11-23). N is defined as an integer > 0 and m denotes 0 or 1 (col. 1, lines 66-67). Generally, the substance with the smaller particle size and present in a smaller amount is the active agent (col. 2, lines 29-33). Preferably the active substances are selected from among betamimetics, anticholinergics, corticosteroids, and dopamine agonists (col. 4, lines 15-18 and 21). Preferred betamimetics are **formoterol (as the fumarate)** and salmeterol, optionally in form of their pharmaceutically acceptable acid addition salts and **hydrates** (col. 4, lines 59-63 and col. 5, lines 12-13). **Preferred corticosteroids include budesonide**, wherein

budesonide and fluticasone are especially preferred (col. 5, lines 42-48). The particularly preferred excipient is **lactose monohydrate** (col. 6, lines 42-44).

***Ascertainment of the Difference Between Scope the Prior Art and the Claims***

***(MPEP §2141.012)***

Walz lacks the express teaching of the order in which the actives are combined with the carrier. This deficiency is cured by the teachings of Keller.

***Finding of Prima Facie Obviousness Rational and Motivation***
***(MPEP §2142-2143)***

It would have been obvious to a person of ordinary skill in the art to combine the teachings of Walz and Keller, because Keller teaches moisture resistant dry powder formulations comprising betamimetics in combination with anticholinergics and/or corticosteroids. A skilled artisan would have been motivated to combine the teachings of Walz and Keller to obtain dry powder formulations comprising betamimetics that are moisture resistant and are present in the form of a salt or ester, such as formoterol fumarate. A skilled artisan would have also been motivated to combine the prior art teachings of Walz and Keller, because both inventors teach inhalable dry powder compositions comprising betamimetics and the inclusion of magnesium stearate in Walz's compositions would be expected to provide these with improved storage stability, and a reduced influence of penetrating moisture on the fine particle fraction (FPF) and fine particle dose (FPD) of said dry powders. A skilled artisan would have had a reasonable expectation of success upon combination of the prior art references because both teach the preparation of dry powder formulations comprising the mixing of dry particulate active(s) with

particulate carrier (e.g. lactose). Regarding the order in which the different components are combined, Keller teaches that the different ingredients can be mixed in any desired sequence. This teaching encompasses the following sequence of steps: blending a portion of 1st active particles with carrier particles to obtain a 1st mixture; combination of a 2nd active with the 1st mixture to obtain a second mixture; and finally admixture of the remaining 1st active particles to obtain a dry powder formulation. Mixing particulate components to obtain a dry powder composition is known as demonstrated by the cited prior art references.

### *Response to Arguments*

Applicant's arguments with respect to claims 1-15 have been considered but are moot in view of the new ground(s) of rejection.

### *Conclusion*

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Musa, US 2003/0133880, is relevant, because it teaches powdery pharmaceutical compositions for inhalation in which the carrier is lactose, the actives may be formoterol or budesonide, and the surface of the carriers is partially coated with lubricant and active particles (title, abstract, [0015]-[0016], [0033], [0035], and [0036]).

Staniforth, US 2006/0029552, is relevant because it teaches carrier particles for use in dry powder inhalers, in which the powders are made in such a way that the active particles adhere to

the surface of the carrier particles and active particles may include beta-2-agonists and steroids as actives (title, abstract, [0051]-[0052], [0075], and [0091]-[0092]).

**Claims 1-15 are rejected. Claims 13-14 are objected. No claims are allowed.**

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, 9:00-6:30, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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